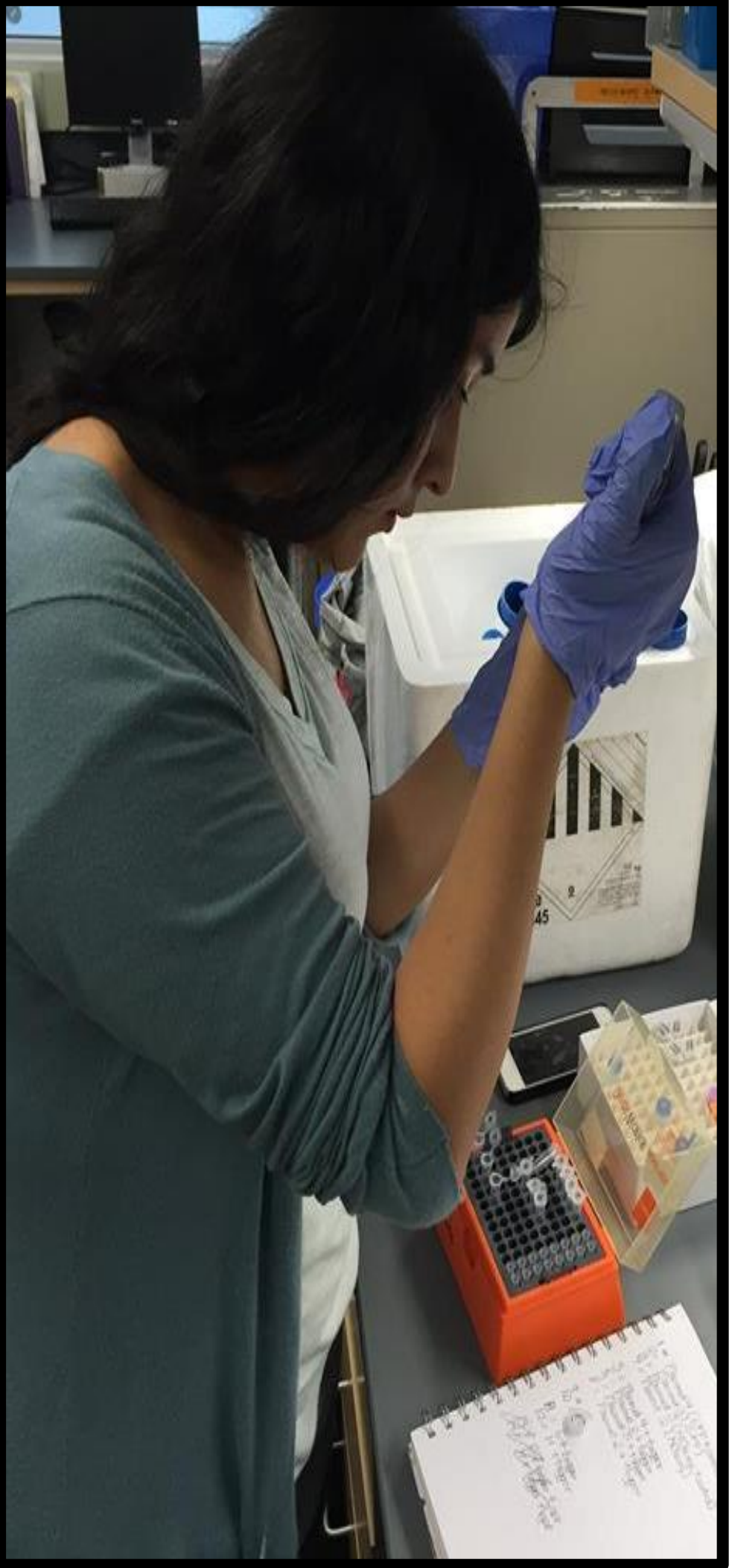


BENCH TO BEDSIDE GUIDE

How to Bring a Diagnostic Test onto the U.S. Market

Written by Robin Pearce

MICHIGAN SYNTHETIC BIOLOGY TEAM

Table of Contents

Disclaimer: The information contained in this guide is not intended as a substitute for professional legal advice. Use it as a general guide on how to bring a diagnostic test onto the U.S. market.

Market Analysis

Clinical Need

The first step in bringing a diagnostic test to market is to evaluate the clinical problem and decide whether or not the product is actually needed. It is imperative that a new diagnostic test improves patient care. The improvement should be substantial enough to warrant the time and expense required to bring a device to market [1]. It is also important not to invent a problem for the sole purpose of implementing new technology to solve it [1]. This leads to the creation of products that are technically advanced, yet serve no practical purpose [1]. Once you have established that your device addresses a significant clinical needed and is an improvement over existing methods, the next step is to advance to market analysis.

Demographic Segmentation and Target Market Selection

The first step in analyzing the market is to realize that it is not homogenous. That is, the market is composed of many different populations. The goal of demographic segmentation is to split a heterogeneous population into relatively homogenous clusters. Each cluster will have different needs and different strategies will be effective for different groups. A marketing strategy that works on one group may not work on another. Furthermore, in the realm of diagnostic tests, a test may not be universally applicable. If a disease/condition only affects certain groups of people, marketing outside of those groups would not produce any additional gains. In fact, it would most likely lead to the incursion of superfluous costs. There are five steps to market segmentation:

Step one: Identify the larger market

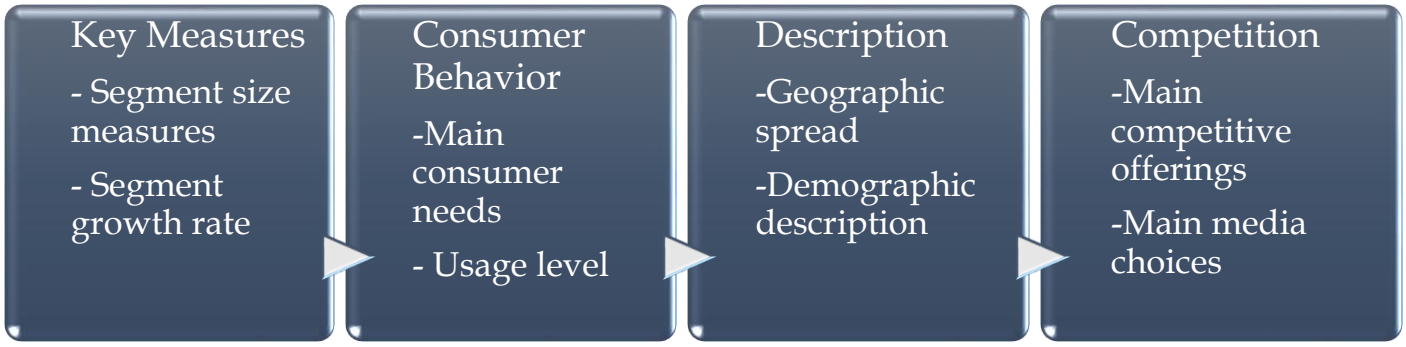
Identifying the larger market includes considering all groups who would find your diagnostic device useful. For example, if you develop a new test for cancer, the larger market might be hospitals with cancer centers. It is important to not define the larger market too broadly. For instance, it may be unwise to market your cancer diagnostic test to a small walk-in clinic that does not specialize in cancer care.

Step two: Create market segments

Once the larger market has been defined, the next step is divide it into smaller homogenous clusters. The market may be segmented based on a number of different criteria. These include geographic regions, socioeconomic status of the population, age, sex, and even country (for international products). A sample market segment for a pregnancy test may be middle class, mothers between the ages of 25 and 40.

Step three- Construct segment profiles

Segment profiles are detailed descriptions of each market segment. Segment profiles may include information on consumer needs, behavior, and usage level. The purpose of segment profiles is to better understand the needs and characteristics of each segment. An example of what should be included in a segment profile is shown in the table on the next page.



Step four: Evaluate market segments for viability

After you have divided the larger market into segments and characterized them, it is essential to make sure that the segments are viable markets. Use the following criteria to evaluate the viability of each segment.

- Homogenous- Potential customers in each segment should be unified by a common factor. This is the crux of market segmentation: each group should be similar enough so that the same marketing strategy is effective within the group.
- Heterogeneous- Each segment should be internally homogenous but distinct from other segments. If this condition is not met, the market has not been successfully segmented.
- Measurable- There should be a way to quantify the size and value of each segment. Without this capability, it is impossible to determine which sections are the best to select as target markets.
- Substantial/Profitable- Each segment should be large enough to make them worth targeting. This criterion is important to determine which markets are large enough to yield a suitable financial return.
- Accessible- Market segments should be evaluated based on whether or not they are accessible in terms of marketing and distribution.
- Practical- It should be possible to market to and sell your product to each market segment.
- Responsiveness- Each market segment should positively respond to distinct market plans rather than mass marketing techniques. If this is not the case, the segments for which similar plans will work may be combined.

Step five: Select the best target markets

After you have divided the market into segments, characterized them, and analyzed the attractiveness of each segment, the final step is to select the target markets that you will go after. The target markets that you choose should be the ones that will yield the greatest return on investment.

Source for all of the information in the Demographic Segmentation and Target Market Selection: [2]

Competition

An integral component of market analysis is analyzing the competition present in the market. The first step in analyzing the competition is to list out the competition and what services/products they offer [3]. Often times, this list includes your major competitors, but there may be others who compete with you indirectly. These included companies that offer products that compete for the same customer capital as you [3]. It is also a good idea to include information on companies who will be entering the market in the coming year [3]. Once you have an idea of who the competition is, the next step is to determine the market share each competitor has [4]. This will allow you to determine who the main competitors are and the size of the market they own. You should also analyze the products and services they provide. In addition to listing your competitors' services and products, it is vital to determine their strengths and weaknesses [4]. This includes considering what makes their products valuable and what services or products are contributing to their growth [4]. Learning the strengths and weaknesses of the competition will enable you to take advantage of what made them successful, while avoiding their pitfalls. From here, you should determine the past, present, and future strategies of these competitors to better understand the trends in the market [4]. Understanding market trends will help you decide if the market will expand or shrink, and whether or not your place in the market will be crowded out. A SWOT analysis, shown below, can be an excellent starting point when analyzing the competition. SWOT analyses involves assessing your strengths and weaknesses as well as opportunities and threats.

Strengths • What give you an advantage over your competitors?	Weaknesses • What places you at a disadvantage relative to your competitors?
Opportunities • External chances to gain a foothold in the market	Threats • External factors that may negatively impact you or act as barriers

Barriers to Enter the Market

Often times, there are many barriers that stand in the way of even entering the market. This is especially true for diagnostic test as they are subject to a great deal of regulation and must be IP protected. These processes take large amounts of time and capital and prohibit many devices from entering the market. In order to overcome these challenges, individuals or companies must apply for grants or attract investors to raise a large amount of capital [5]. Even if companies raise sufficient funds, there is no guarantee that they will be successful. A number of different situations could potentially sideline a diagnostic test. For instance, the test could already be patented by somebody else, thus excluding others from producing it. Even if the test is not patented, this does not rule out the possibility of legal litigation. It is estimated that the average cost of patent litigation is greater than $2 million [1]. Moreover, the FDA could deny the

premarket submission on the grounds that the device is not safe and/or effective. If the device is not FDA approved, then it cannot be marketed in the US. Additionally, startup companies may not have access to distribution channels that can produce and distribute their product [5]. Furthermore, incumbent products may dominate the market, preventing new products from ever gaining a foothold [5]. Truthfully, there are many barriers involved when bringing a diagnostic test to market. A helpful tool to examine some of these barriers and other aspects of the market is the PEST analysis (shown below). The PEST analysis examines the effects that political, societal, economical, and technological forces have on the market [6].

Political • Information on the government's role in the economy. • Includes tax policy, regulations, and tariffs.	Social • Information on how societal factors influence the economy. • Includes population growth rate, attitudes, and health consciousness
Economical • Information on economic factors. • Includes economic growth rate, inflation, unemployment rate, GDP, and per capita income.	Technological • Information on how technology issues affect the economy and the way you deliver your services to the marketplace. • Includes technological advancement, government spending on technology, and life cycle of current technology.

[6]

IP Protection

Patent Definition

An important aspect of bringing your diagnostic test to market is preventing others from stealing your idea. This is where patents come into play. According to the U.S. Patent and Trademark Office (USPTO), a patent is the grant of a property right to the inventor, issued by the United States Patent and Trademark Office [7]. Patents grant the holder the right to exclude other from making, using, or offering for sale the device within the US, US territories, and US possessions [7]. Utility patents generally last for 20 years from the date of application [7]. It is often a very good idea to hire a patent attorney who can guide you through the process of patenting your diagnostic test. For a list of patent attorneys, search the USPTO's roster of attorneys found here.

Device Patent Eligibility

Before filing for a patent, it is necessary to determine whether or not the device is patentable. The patent law states that anyone who "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent" [8]. To be useful, a device must have both a valuable purpose and also perform the intended purpose as stated [8]. A device that is unable to perform its intended purpose would not be considered useful, and, therefore, would not be patentable. Additionally, patents require a complete description of the device, so a mere idea or suggestion cannot be patented [8].

As stated above, in order for a diagnostic test to be patented, it must be "new." Thus, novelty is a major requirement for patentability [8]. Consequently, nothing that was invented after an equivalent item was known or used in the US, or patented/described in a printed publication in the US or a foreign country may be patented [8]. Inventors are also unable to acquire a patent if the application is filed more than one year after public sale or use of the invention in the US or if the device is described in a printed publication in the US or abroad [8]. This implements a one-year grace period, in which the inventor is able to obtain a patent within a year of public disclosure of his/her invention [8].

While trying to determine if a device is novel, it is imperative to conduct a patent search. A patent search involves searching issued patents and published patent applications to find any patents that are the same as your device. The USPTO recommends a seven step strategy for conducting a patent search. These seven steps are outlined on the next page in the Patent Search section.

In addition to novelty, a device must also be non-obvious [8]. That is, the invention must be a substantial improvement over any previously patented devices. An invention is said to be non-obvious if the improvement would not be obvious to a person with "ordinary skills in the art" to which the device pertains [8]. Essentially, this means that if the invention is obvious to a person with average skills in the type of technology used to create it, it fails to meet the non-obvious criterion [8]. Determining whether a device is obvious or not is often a very difficult decision. The decision involves an examiner from the patent office reviewing previous patents that are similar to the submitted invention [8]. If all of the features of the submitted invention are found in one patent, then the request will be rejected for failing to fulfil the novelty requirement [8]. If all of the features cannot be found in one patent, then the examiner will determine whether or not the features can be covered by combining multiple previously patented devices [8]. If the examiner finds this

to be the case, the patent will often be rejected on the grounds of being an obvious combinations of multiple inventions [8].

Not only must the invention meet various requirements to be patentable, the filer must also meet certain requirements to file a patent application. In general, the inventor of a device may patent it [9]. Others may also apply for patents under certain conditions. If the inventor assigns the invention to another person, the person to whom the invention is assigned may apply for a patent [9]. If the inventor dies, the executor of the estate may apply for a patent [9]. If the inventor is legally incapacitated, the legal representative or guardian may apply for a patent [9]. If the invention was developed by multiple people, they may apply for a patent as joint inventors [9]. Note that people whose only contribution is financial may not be listed as inventors [9]. Interestingly enough, employees of the U.S. Patent and Trademark Office are forbidden from applying for patents; however, they may inherit a patent [9].

Types of Patents

There are three types of patents: utility patents, designs patents, and plant patents. Five categories of inventions fall under utility patents. These include processes, machines, compositions of matter, improvements of existing ideas, and manufactures. Utility patents last for 20 years after the date the application is filed. Diagnostic tests fall under the category of utility patents. The second type of patent is the design patent. Design patents protect designs that ornament an article of manufacture. Articles that are protected by design patents include the design of specific brands of furniture or wallpaper. Design patents protect the aesthetic aspect of a design and do not cover any functional characteristics. Design patents last for 14 years. The third and final type of patent is the plant patent. Plant patents protect novel asexually reproducible plants. Asexual reproduction is defined as "propagation of a plant to multiply the plant without the use of genetic seeds to assure an exact genetic copy of the plant being reproduced" [10]. Plant patents exclude others from asexually reproducing, selling, or using the patented plant for 20 years from the date of application of the patent.

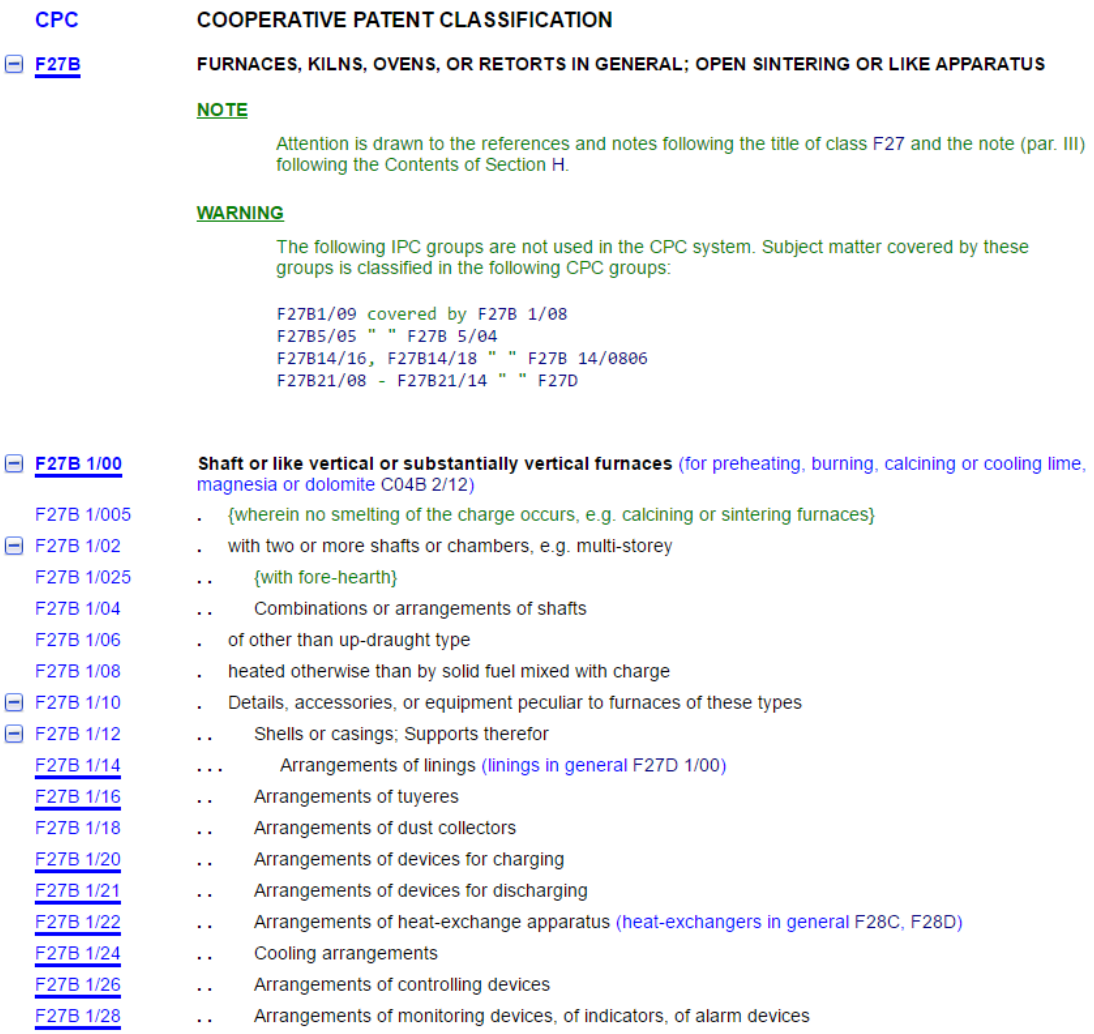
Source for all of the information in the Types of Patents section: [10]

Patent Search

The USPTO recommends the following seven step strategy when conducting a patent search.

1. **Brainstorm terms describing your invention**- Think of terms that describe your invention based on its purpose, components, and use.
2. **Access and review cooperative patent classification schema using USPTO's website site search feature**- Use the terms you just brainstormed to find initial Cooperative Patent Classification (CPC) using USPTO's website (www.uspto.gov). To do this, in the search box at the top right corner of USPTO's website, type in "CPC Scheme [keyword(s) describing invention]". For example, if you wanted to find CPC for patents related to ovens, you would type in "CPC Scheme oven." Go through the results to determine the most applicable classification for your device. The CPC search for ovens yields the below

results. The classification term is found under the CPC column. The first letter corresponds to the section. The next two digits are the class and the next letter is the subclass. The next one to two digits before the slash indicate the group and the last digits after the slash indicate the main group or subgroup. For the CPC F27B 1/00, F is the section, 27 is the class, B is the subclass, 1 is the group, and 00 is the main group. If the group number was 1/01 instead of 1/00, 01 would be the subgroup (00 indicates the main group).



CPC — COOPERATIVE PATENT CLASSIFICATION

F27B — FURNACES, KILNS, OVENS, OR RETORTS IN GENERAL; OPEN SINTERING OR LIKE APPARATUS

NOTE

Attention is drawn to the references and notes following the title of class F27 and the note (par. III) following the Contents of Section H.

WARNING

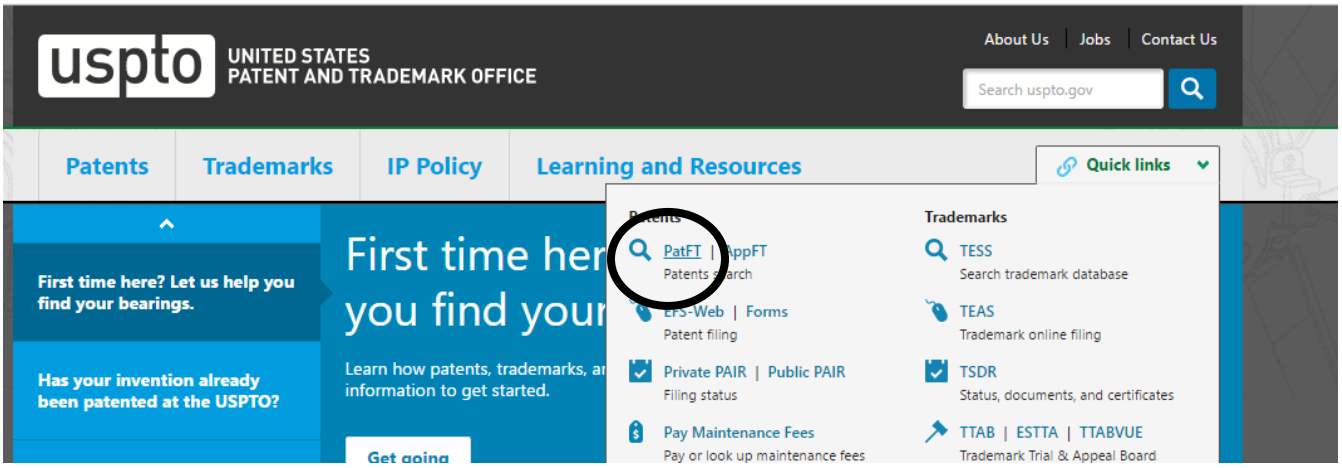
The following IPC groups are not used in the CPC system. Subject matter covered by these groups is classified in the following CPC groups:

F27B1/09 covered by F27B 1/08
F27B5/05 " " F27B 5/04
F27B14/16, F27B14/18 " " F27B 14/0806
F27B21/08 - F27B21/14 " " F27D

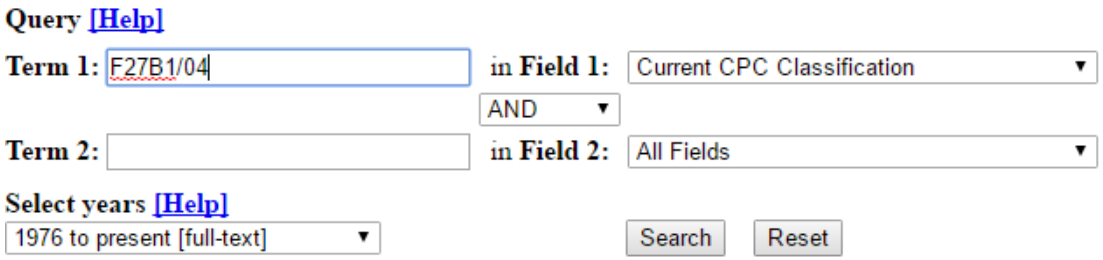
F27B 1/00		**Shaft or like vertical or substantially vertical furnaces** (for preheating, burning, calcining or cooling lime, magnesia or dolomite C04B 2/12)
F27B 1/005	.	{wherein no smelting of the charge occurs, e.g. calcining or sintering furnaces}
F27B 1/02	.	with two or more shafts or chambers, e.g. multi-storey
F27B 1/025	..	{with fore-hearth}
F27B 1/04	..	Combinations or arrangements of shafts
F27B 1/06	.	of other than up-draught type
F27B 1/08	.	heated otherwise than by solid fuel mixed with charge
F27B 1/10	.	Details, accessories, or equipment peculiar to furnaces of these types
F27B 1/12	..	Shells or casings; Supports therefor
F27B 1/14	...	Arrangements of linings (linings in general F27D 1/00)
F27B 1/16	..	Arrangements of tuyeres
F27B 1/18	..	Arrangements of dust collectors
F27B 1/20	..	Arrangements of devices for charging
F27B 1/21	..	Arrangements of devices for discharging
F27B 1/22	..	Arrangements of heat-exchange apparatus (heat-exchangers in general F28C, F28D)
F27B 1/24	..	Cooling arrangements
F27B 1/26	..	Arrangements of controlling devices
F27B 1/28	..	Arrangements of monitoring devices, of indicators, of alarm devices

3. **Review classification definition linked to the CPC classification you selected-** This is important to determine if the CPC classification you selected is the most relevant classification. The CPC classification definition can be found to the right of the CPC classification in the above figure. For instance, the classification definition of F27B 1/04 is “Combinations or arrangements of shafts.”

4. **Retrieve and review issued patents using the CPC classification you selected-** Once you have determined the appropriate classification, the next step is to review issued patents that fall under the same classification. To do this, go to UPTO's homepage and under Quick Links select PatFT (see figure below).



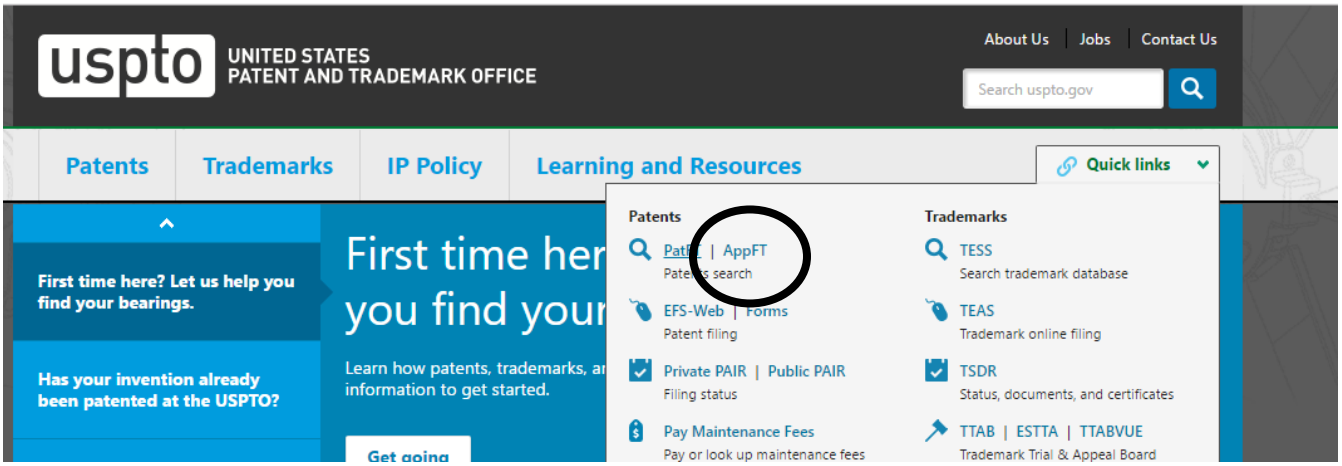
In the next page, type in the CPC classification in the Term 1 box and select "Current CPC Classification" in the Field 1 box. Do not enter the space in the middle of the CPC classification (see figure below for an example).



This search will show all patents that fall under the given CPC classification. Click on the title of one of the patents that come up and then click on the "Images" button at the top of the page to view the PDF version of the patent. Review the front page information of each patent, carefully considering the abstract and drawings to determine if the inventions are similar to yours. Write down the patent numbers of patents that are similar to yours.

5. **Conduct in-depth review of patents you selected based on their front-page information-** Go back over in detail any patents for inventions that are similar to yours. Pay close attention to the claims of the patent, as they are the boundaries of legal property rights given to the patent holder.

6. **Retrieve and review published patent applications using the CPC classifications you identified-** After you have reviewed issued patents that are fall under the same CPC classification, the next step is to review all patent applications that have the same CPC classification. To do this, follow the same steps as you did in step 4, except instead of clicking on PatFT, click on AppFT (see figure below).



After clicking on AppFT, type the same CPC classification number in the Term 1 box as you did in step 4 and select Current CPC Classification in the Field 1 box. This search will give you all of the current patent applications that fall under your CPC classification. As in step 4, review the front page of each application and write down all the applications that are similar to your invention. Next, conduct an in-depth review of each application, paying special attention to the "Claims" section.

7. **Options for broadening your search**- If you are unable to find relevant publications, you can try broadening your search. There are a number of ways this can be done. Instead of searching the PatFT and AppFT databases by CPC classification, you can search using keywords. You can also search the European Patent Office's worldwide patent publication database (https://worldwide.espacenet.com) using the CPC classification for your invention. Since inventions may be publically disclosed a number of different ways, you can search books, journal articles, websites, and other places to determine if there are already similar inventions. It may also be a good idea to hire a patent attorney who can provide professional expertise and conduct a second patent search.

Source for all of the information in the Patent Search section: [11]

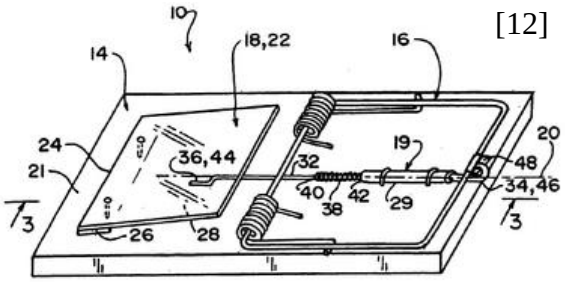
Provisional Utility Patents

Provisional patents are used to establish an early effective filing date for nonprovisional patent applications. They also enable the filers to apply the phrase "Patent Pending" to their product. Furthermore, they curtail the risk of having the invention stole by others before a nonprovisional application is filed. The benefits of provisional patents last for one year. After this period, the priority benefits expire and the filer is considered to have abandoned the idea. Provisional patents do not result in patents unless a nonprovisional application is submitted that claims the benefits of the previously filed provisional patent. Additionally, an individual may file a petition to change the provisional application into a nonprovisional application. Converting a provisional patent application into a nonprovisional patent application, will decrease the terms of the patent. If a separate nonprovisional application is filed after a provisional patent, the terms of the patent can

be extended by 12 months. Provisional patents are not evaluated based on their merit, so it is unnecessary to include claims or a disclosure statement identifying similar patented devices.

It is important that a provisional patent include all of the required content. If not, the benefit of having an earlier effective filing date for nonprovisional patents may be forfeited. Moreover, the earlier effective filing date may be forfeited if the information contained in the provisional application does not match the information contained in the nonprovisional application. Provisional applications require a specification of the design and at least one drawing of the device. The required specifications are outlined in 35 U.S.C 112. The specifications must include a written description of the device and the process by which the device is to be made and used. The description must be detailed enough that a person skilled in the technology used to create the device would be able to make and use it. The description should also include the best mode the inventor knows for carrying out the invention. This prevents inventors from concealing the best uses of their device.

[12]



Example patent drawing from U.S. Patent No. 6,655,077, titled "Trap for a mouse."

Provisional patent applications must include at least one drawing where necessary for the understanding of the device. See the figure to the right for an example of a patent drawing. It is common practice to include as many drawings as are necessary to understand the device. In fact, most patent applications contain several sheets of drawings. However, patents for chemical compounds/compositions and processes do not require drawings. There are a number of highly specific requirements for patent drawings. These include such requirements as the size of the sheet of paper and the minimum dimensions of the margins. These requirements can be found here.

Provisional applications must also include a filing fee and cover sheet. The filing fee is subject to change annually. The current fee can be found at www.uspto.gov. The cover sheet must demarcate the application as a provisional application and include the names of all inventors, the residences of the inventors, the title of the invention, name and registration number of the attorney, correspondence address, and information on any U.S. Government agencies that have property interest in the application. The cover sheet for a provisional application can be found here.
Provisional patent applications can be filed by mail or electronically. If you choose to file by mail, send the provisional application papers, including the written description of the device and any drawings, as well as the cover sheet and filing fee to the following address:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applications may also be filed electronically using EFS-web. The documents can be filed as a PDF and the fee can be payed online. More information on EFS-web can be found here.

Source for all of the information in the Provisional Utility Patent section: [12]

Nonprovisional Utility Patents

Nonprovisional utility patents grant the holder the right to exclude other from making, using, or offering for sale the patented invention within the US, US territories, and US possessions. Utility patents generally last for 20 years from the date of application. A nonprovisional utility patent should include the following items.

- Transmittal form
- Application data sheet
- Specifications (with claim(s))
- Drawings
- Executed oath or declaration
- Nucleotide and amino acid sequence (if applicable)
- Large tables or computer listings (if applicable)

Transmittal Letter

Transmittal forms identify the items being filed such as the specifications, claims, drawings, declaration, and disclosure statement. The form also lists applicant(s), the type of application, and the title of the invention. Transmittal forms or letters must be filed with each patent application. The transmittal form can be found here.

Application Data Sheet

Filling out an application data sheet is recommended for all nonprovisional applications and is required when the filer wants to claim the benefits or priority of previously filed provisional applications or foreign applications. Application data sheets must be titled “Application Data Sheet” and contain the following information:

- Inventor information- The sheet must contain each inventor’s legal name, residence, and mailing address.
- Correspondence information- A correspondence address must be included.
- Application information- This section should include the title of the invention, the number of drawing sheets, docket number assigned to the application, type of application (utility patent), whether the application contains information under a secrecy order, and references to the previously filed foreign or provisional applications. The previously filed application’s filing date, application number, and country of origin (if applicable) should be included as part of this requirement.
- Representative information- This section should contain the registration number and other information on each person who has the power of attorney in the application.
- Domestic benefit information- “This information includes the application number, the filing date, the status (including patent number if available), and relationship of each application for which a benefit is claimed under 120, 121, 365(c), or 386(c). Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120 and § 1.78.”
- Foreign priority information- This should include the application number, country, and filing date of each foreign application that the submitter is claiming priority for. This satisfies the claim of priority required by 35 U.S.C. 119(b) and § 1.55.

- Applicant information- This information should include the name and address of the legal representative or person who has been assigned the invention.

The form for the application data sheet can be found here.

Specifications

The required specifications are outlined in 35 U.S.C 112. The heading of the first page of the specifications should be the title of the invention. The specifications must include a written description of the device and the process by which the device is to be made and used. The description must be detailed enough that a person skilled in the technology used to create the device would be able to make and use it. The description should also include the best mode the inventor knows for carrying out the invention. This prevents inventors from concealing the best uses of their device. If the patent application is for an improvement of an existing device, the submitter must focus on describing the specific improvement(s). The specifications must end with one or more claims that lay out what the inventor considers the invention. The claims section must begin on a separate page and be numbered in Arabic numerals. Claims define the scope of protection that is sought in the patent application. An example claim is shown below.

"1. A golf bag security system for detecting movement of at least one golf club in a golf bag, the golf bag security system comprising:

a. a detection loop substantially arranged around the circumference of a golf bag
b. a loop oscillator circuit, connected to the detection loop
c. a control circuit, capable of detecting a change in inductance in the loop, identifying an alarm condition in response to the change of inductance, and
d. an alarm device responsive to the alarm condition [14]."

Material submitted on a separate compact disc must be referred to in the specifications. Information that may be submitted on a separate CD include computer program listings, gene sequence listings, and tables of information. Computer program listings should follow the guidelines detailed in 37 CFR § 1.96(b) and (c). All information submitted on a CD must be in compliance with 37 CFR § 1.52(e).

The specification section should be organized under the following sections headings:

- Statement regarding federally sponsored research or development- "This section should contain a statement as to rights to inventions made under federally sponsored research and development (if any). See MPEP §310 for more information."
- Reference to sequence listing, a table, or a computer program listing compact disc appendix
- Background of the invention- This section should contain a statement of the field to which the invention belongs and subject matter of the device. Also included in this section are references to specific documents relevant to your invention and problems with previous related inventions.
- Brief summary of the invention- This section should include a summary of the general idea of the invention and how it solves existing problems.
- Brief description of different drawing views- This section should contain a list of all figures by number and statements that explain what each figure depicts.

- Detailed description of the device- This is the section that includes an explanation of the process of making and using the device and the best mode of use.
- Claim(s)
- Abstract of the disclosure- The abstract points out the features of your invention that are novel. The abstract should be no longer than 150 words.

Drawings

Utility patent applications must include at least one drawing where necessary for the understanding of the device. It is common practice to include as many drawings as are necessary to understand the device. In fact, most patent applications contain several sheets of drawings. Drawings should be included for every feature specified in the claim(s). Patents for chemical compounds/compositions and processes do not require drawings. There are a number of highly specific requirements for patent drawings. These include such requirements as the size of the sheet of paper and the minimum dimensions of the margins. These requirements can be found here.

Executed Oath or Declaration

Each inventor must sign an oath that he/she believes him/herself to be an original inventor or joint inventor of the device in question. The form for the oath can be found here. For a deceased inventor, his/her legal representative may fill out the oath. If the inventor is unable to be found, any joint inventor may fill out the oath for him/her. In either of these cases, the substitute oath form can be found here.

Sequence Listing

This section should contain a listing of the nucleotide or amino acid sequences used in the device, if applicable. The sequence listing must comply with the requirement set forth by 37 CFR §1.821 through 37 CFR §1.825.

Filing a Nonprovisional Utility Patent

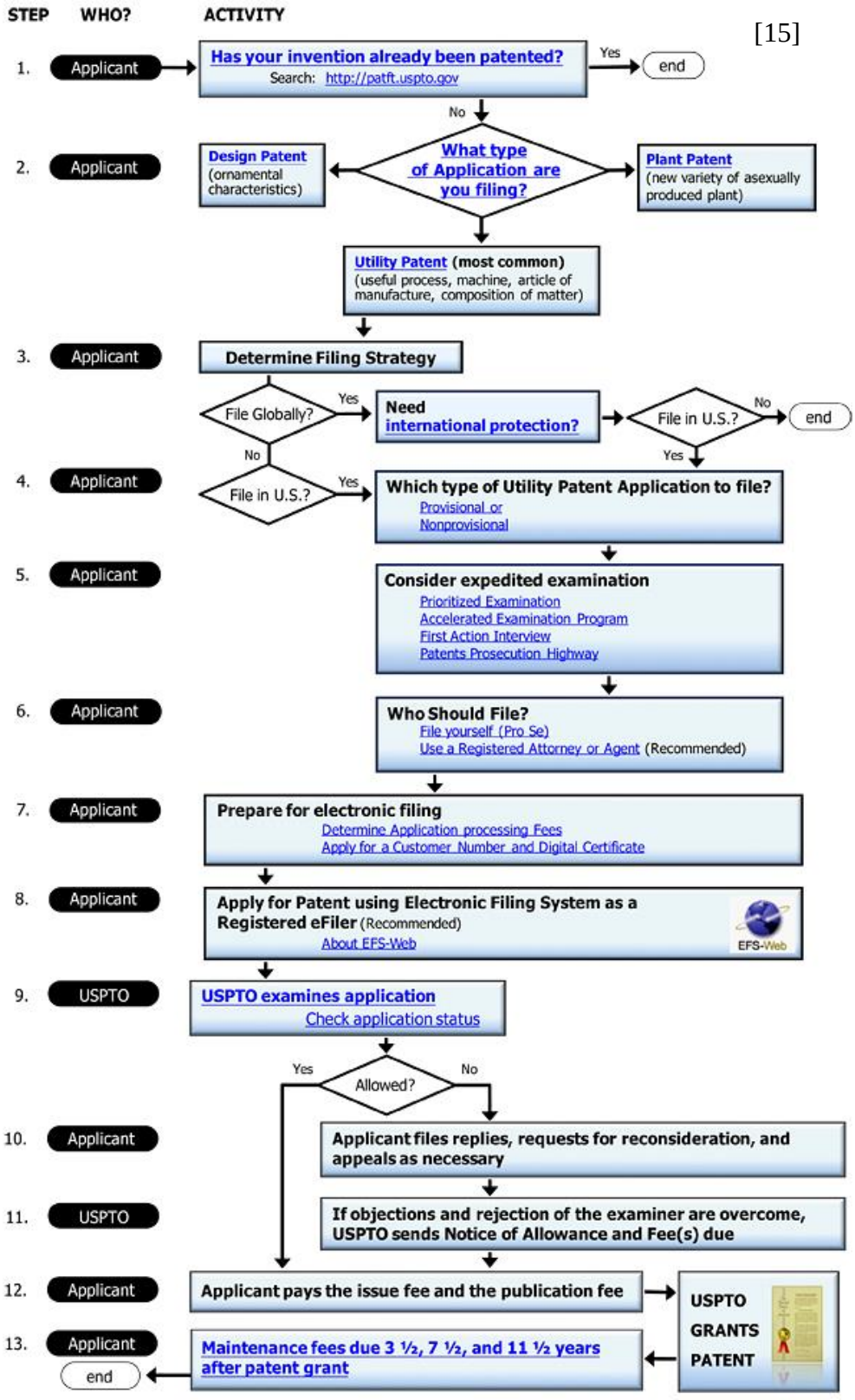
It is recommended that nonprovisional utility patents be filed electronically through EFS-web. More information on EFS-web can be found here. If the filer does not submit the application electronically, he/she must pay a $400 non-electronic filing fee. To check on the status of the submitted application, the person who filed the application may attach a postcard to the front page of the documents. The postcard should contain a detailed list that identifies each type of document and the number of pages of each document. In addition, the submitter should include the application number, confirmation number, filing date of the application, title of the invention, and name(s) of the inventor(s) on the postcard. When the USPTO receives the application, the list on the postcard will be compared to what was actually received. Any discrepancies will be noted on the postcard. The postcard, with notes, will be returned by mail to the addressee whose name appears on the postcard.

Example nonprovisional patents can be found by following the procedures described in the patent search section

Unless otherwise noted, source for all of the information in the Nonprovisional Utility Patents section: [13]

Process for Obtaining a Nonprovisional Utility Patent

[15]



IP Protection and Universities

If you patented your idea while working for or as a student of a university, it is important to consider your university's IP policies. In general, each university's policies are different. To give an example of a specific university's policy, the University of Michigan's policies will be highlighted.

According to UM's IP policy, "Under U.S. copyright law, the University holds the copyright (as "works made for hire") in copyrighted works authored by its EMPLOYEES who are acting within the scope of their employment. Otherwise, the University does not hold copyright in a work, unless the copyright has been transferred legally to it by written assignment or other process of law" [16] At UM, IP made by any person with direct or indirect funds from the University, is owned by the University. Funds include employee compensation, materials, and facilities. As a general rule, the University will not claim the IP rights of students, unless the IP is created in the student's capacity as an employee. The University will claim ownership of IP developed by faculty on sabbatical if they receive a salary during the sabbatical. Moreover, UM claims ownership of IP developed by former employees if the IP was made with substantial University faculty guidance/resources and during activities directly relating to employment.

Employees are expected to report any IP to the Office of Technology Transfer (OTT). They are also obligated to report the names of all inventors and people that contributed to the making of the IP. If an employee believes that his/her IP does not fall under University ownership, he/she should submit a brief written summary of the invention and the circumstances of the invention to OTT. The employee should also wait for at least thirty days after submitting the information to OTT before bringing the invention to market. The aforementioned disclosure is unnecessary if the employee has a reasonable belief that the IP is the result of work that clearly falls outside of his/her field of work/responsibilities or for scholarly works. UM defines scholarly works as "works authored by FACULTY within the scope of their employment as part of or in connection with their teaching, research, or scholarship" [16]. Examples of scholarly works include lecture notes, textbooks, and course material.

After UM recovers its expenses, the revenue generated from royalties and sale of equity interests are distributed as shown on the right.

Up to $200,000: [16]
50% to the Inventor(s)
17% to the Inventor's department
18% to the Inventor's school or college
15% to the central University administration

Over $200,000 (and up to $2,000,000):
30% to the Inventor(s)
20% to the Inventor's department
25% to the Inventor's school or college
25% to the central University administration

Over $2,000,000:
30% to the Inventor(s)
35% to the Inventor's school or college
35% to the central University administration

IP rights may be granted back to inventors. In these cases, the University recovers its expenses in addition to 15% of any royalties, equity, or other value received by the inventors through their use/licensing of the IP.

Source for all of the information in the IP Protection and Universities section: [16]

FDA Regulations

What is an *In Vitro* Diagnostic Product?

Before a diagnostic test can ever be marketed, it must meet various regulatory standards put forth by the FDA and other agencies. The FDA defines an *in vitro* diagnostic product (IVD) as "those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body" [21 CFR 809.3].

Regulations surrounding *in vitro* diagnostic products are put into place to ensure that they are safe and effective. The FDA refers to safety and effectiveness in the following ways:

- Safety: Are there reasonable assurances based on valid scientific evidence that probable benefits to health from use of the device outweigh any probable risks? [21 CFR 860.7 (d)(1)]
- Effectiveness: Is there reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results? [21 CFR 860.7(e)(1)]

Classes of *In Vitro* Diagnostic Devices

Under Section 513 of the Federal Food, Drug and Cosmetic Act, the FDA divides IVDs into three different classes:

Class I	• Low to moderate risk • Regulations: general controls
Class II	• Moderate to high risk • Regulations: general and special controls
Class III	• High risk • Regulations: general controls and PMA

- **Class I**- Class I devices present low to moderate risk. Class I devices are devices for which the general controls presented in sections 501, 502, 510, 516, 518, 519, or 520 of the Federal Food, Drug, and Cosmetic Act are sufficient to ensure the safety and effectiveness of the device. If it is unknown whether or not the device can be safely regulated by the general controls, the device may still fall under class I if it meets several requirements. The device must not present a potential unreasonable risk of illness or injury and it may not be used to support/sustain human life or for a use which is of substantial importance in preventing impairment of human health.

Examples of Class I IVDs [18]
- Lactic acid test
- Erythrocyte sedimentation rate test
- Differential culture media

- **Class II**- Class II devices present moderate to high risk. Class II devices are devices for which the general controls alone are insufficient to assure safe and effective use. In these cases, special controls must be instituted. These controls include the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and any other action the Secretary deems necessary. If the device is purported to be used to support or sustain human life, the Secretary must identify additional necessary controls and how they provide assurance of the safe and effective use of the device.

Examples of Class II IVDs [18]
- Factor deficiency test
- Antimicrobial susceptibility test systems
- Thyroid stimulating hormone test system

- **Class III**- Class III devices present high risk. Class III devices are devices for which insufficient information exists to determine whether or not they can be safely regulated by the general controls or the special controls used for class II devices. Moreover, class III devices present a potential unreasonable risk of illness or injury and are purported to be used to support or sustain human life or be of substantial importance in preventing impairment of human health. Class III devices must obtain premarket approval (PMA). PMAs will be reviewed in greater depth in the next section.

Examples of Class III IVDs [18]
- Hepatitis B and C, HPV tests
- Total PSA for prostate cancer screening
- Continuous Glucose Monitoring Devices

Note: General controls must be met by all classes of devices and include provisions related to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices.

Unless otherwise noted, source for all of the information in the Classes of In Vitro Diagnostic Devices section: [17]

Five steps to FDA clearance/approval

Step one: Classify your device

It is important to classify your diagnostic as either class I, II, or III according to the guidelines presented in the above section. Although the FDA will officially classify your device when they review your premarket submission, classifying your device will give you an idea as to the submission path you must follow [19]. Additionally, it will help you determine the level of regulatory control your device is subject to [19].

Optional step: Send in a Pre-Submission

Pre-Submissions are not the same as premarket submissions. Pre-Submissions are optional and used to receive feedback from the FDA prior to the submission of an IDE or premarket submission. The FDA may provide advice on clinical studies protocol and what nonclinical studies should be undertaken. Pre-Submissions are especially recommended when the device involves novel technology that the FDA may be unfamiliar with. Pre-Submissions should include the following information:

1. Cover letter- The cover letter should state the reason for the Pre-Submission (Pre-Sub for 510(k), Pre-Sub for PMA, etc . . .) and contain the company name, address, contact person, phone number, fax number, and email address. Lastly, the cover letter should include the name of the device and the signature of the responsible party.
2. Table of contents- Pre-Submissions should include a table of contents. In addition, for paper copies, it is recommended that tabs are used between sections and the pages are sequentially numbered.
3. Device description- This section should contain the following items:
    a. Pictures of the device (if applicable)
    b. Engineering drawings of the device (if applicable)
    c. Processes/principles by which the device works
    d. Physical and biological features of the output (if applicable)
    e. Device samples (if the device is able to be shipped)
    f. Information on how the user will operate the device. This includes an explanation of the user interface.
    g. Discussion on the materials that make up the device
    h. How the device is manufactured (if applicable)
    i. Mechanism of action and how the device/device output are used.
    j. Detailed description of instruments, reagents, components, software, principles of operation, and accessories used and description of any changes to previously approved IVDs.
    k. Scientific basis for development and a discussion of clinical utility.
    l. For Pre-Submissions for 510(k)s, comparison to predicate devices.
4. Proposed intended use/indications for use- This section should include a description of the intended use of the device and may include information on the underlying disease, target population, part of the body the device interacts with, frequency of use, and physiological use. For diagnostic tests, this section should also contain the analyte/condition to detect and the methodology behind the assay.
5. Previous discussions or submissions- Summarize previous submissions for the device or similar devices. When available, submission numbers should be included.
6. Overview of product development- Include an outline of planned nonclinical and clinical studies.
7. Specific questions- Include the specific questions that the submitter has for the FDA. These questions will guide the feedback the FDA provides. Often times, questions focus on data

requirements and pre-clinical and clinical testing protocol. Example questions for each type of Pre-Submission can be found here, starting on page 33.

8. Method for feedback- Specify the preferred method of feedback from the FDA. Feedback may be given through an in-person meeting, teleconference, facsimile, or by email. If an in-person or teleconference meeting is requested, the submission should include the requested meeting format (in-person or teleconference), along with three or more preferred meeting dates and times. For in-person and teleconference meetings, the submission must contain planned attendees, including each attendee's position, or title, and affiliation. Furthermore, a list of any audiovisual equipment needed for the meeting should be included.

Source for all of the information in the Optional step: Send in a Pre-Submission section: [20]

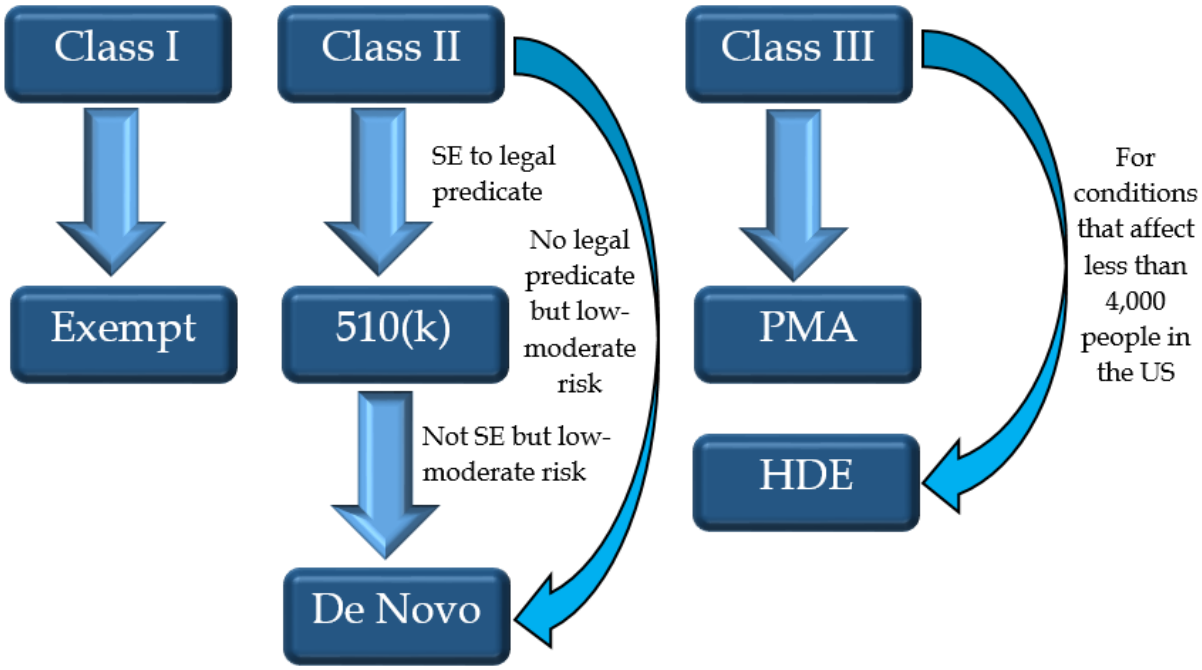
Step two: Select the correct premarket submission

Once your device has been classified, the next step is to select the correct premarket submission. There are four different types of premarket submissions: 510(k), PMA, de novo, and HDE. Note, most class I device do not require a premarket submission

- **510(k)-** Most class II devices require the submission of a premarket notification, commonly referred to as a 510(k). The overall purpose of the 510(k) is to prove that your device is safe and effective and substantially equivalent to an existing, legally marketed device. Legally marketed devices include those that were legally marketed prior to May 28, 1976 and did not require a PMA, devices that have been reclassified from class III to class I or II, and devices that have already been determined to be substantially equivalent via the submission and approval of a 510(k) [21]. Substantial equivalence is granted if the device has same intended use as the legally marketed device (predicate) and the same technological characteristics as the predicate [21]. If the device does not have the same technological characteristics as the predicate, it may also be substantially equivalent if the data provided in the 510(k) demonstrates that the device is at least as safe and effective as the predicate [21].
- **Premarket Approval (PMA)-** Class III devices require the submission of a PMA, the strictest device marketing application required by the FDA [22]. Unlike a 510(k), the purpose of a PMA is not to demonstrate that the diagnostic test is substantially equivalent to an existing, legally marketed product. However, similar to the 510(k), it is used to determine whether or not a device is safe and effective [22]. The key to submitting a successful PMA is to not only fulfill the administrative requirements but to also provide solid scientific support as to why a device is both safe and effective [22]. As such, a PMA must contain a technical section, which includes a non-clinical laboratory studies section and a clinical investigation section [22]. This will be explored in greater depth in the next step.
- **De Novo**- The de novo pathway is useful for obtaining approval of low to moderate risk devices for which there is no valid predicate device [23]. The FDA will generally classify devices that lack predicates as class III, which are subject to strict regulations. A de novo request may be submitted in liu of a 510(k) if the device is so novel that there are no legal

predicates [23]. In this case, approval is based upon a risk-based classification instead of a substantial equivalence determination [23]. A de novo request may also be submitted within 30 days of a not substantially equivalent ruling on a 510(k) [23].

- **Humanitarian Device Exemption (HDE)-** HDEs are intended to be utilized for class III devices used to diagnose/treat diseases that affect fewer than 4,000 individuals in the U.S. [24]. An HDE submission is comparable to a PMA, but it does not require clinical investigations to prove the effectiveness of the device [24]. Nevertheless, the submitter must still prove that the device is safe. Moreover, an HDE must demonstrate that there are no comparable devices to diagnose the disease/condition and that the exemption is required to bring the device to market [24].



Step three: Compile the necessary information for your premarket submission

Once you have determined the appropriate pre-market submission, you must compile the required information.

510(k)

Under 21 CFR 807.87, the following information is required for the submission of a 510(k):

- The proprietary name and the common name or classification name of the device.
- The registration number of the establishment submitting the premarket notification.
- The class (as described in 21 CFR 513) and panel (if known) of the device. If the owner asserts that the device has not been classified under 21 CFR 513, a justification of the determination must be included.

- Action taken to fulfill the requirements of 21 CFR 514 regarding performance standards.
- Proposed labeling that will describe the device, its intended use, and the directions for its use. If applicable, include any photographs or engineering drawings.
- Explanation on how the device is similar to/different from other related products on the market. The explanation should include an identification of the similar products, materials, design considerations, energy expected to be used by the device. This section may also include a description of the operational principles of the device.
- When a person modifies an existing device or propose a new use for it, he/she must provide sufficient data to show that the changes/new application do not result in the device being unsafe or ineffective. The supporting data must show that the manufacturer has considered the consequences the changes/new application have on the safety and effectiveness of the device.
- A 510(k) summary as described in 807.92 or a 510(k) statement as described in 807.93 (Appendix A).
- A financial certification or disclosure statement as outlined in 21 CFR 54.4.
- "For submissions claiming substantial equivalence to a device which has been classified into class III under section 513(b) of the act:
    - Which was introduced or delivered for introduction into interstate commerce for commercial distribution before December 1, 1990; and
    - For which no final regulation requiring premarket approval has been issued under section 515(b) of the act, a summary of the types of safety and effectiveness problems associated with the type of devices being compared and a citation to the information upon which the summary is based (class III summary). The 510(k) submitter shall also certify that a reasonable search of all information known or otherwise available about the class III device and other similar legally marketed devices has been conducted (class III certification), as described in 807.94. This information does not refer to information that already has been submitted to the Food and Drug Administration (FDA) under section 519 of the act. FDA may require the submission of the adverse safety and effectiveness data described in the class III summary or citation."
- "A statement that the submitter believes, to the best of his or her knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted."
- When sufficient information is not provided to make a ruling, the Commissioner will request additional information. The submitter should send the information by itself or in a new premarket submission at least 90 days before the date the owner intends to bring the device to market. If the information is not provided within 30 days, the submission is considered withdrawn.

Source for all of the information in the 510(k) section: [25]

A 510(k) for *in vitro* diagnostic devices must also include studies on performance characteristics. The submission should include studies appropriate for the device as well as descriptions of the protocol and results of each study. Studies should revolve around:

- Precision/repeatability/reproducibility- Precision is a measure of the dispersion of the results for repeated test samples, while reproducibility is defined as "the amount of agreement between replicates (usually two or three) of each sample within a run of the assay, and the amount of between run agreement for the normalized values of each control sample" [26]. On the other hand, reproducibility is the "amount of agreement between results of samples tested in different laboratories" [26]. Repeatability/precision can be measured by comparing normalized results of many runs of the assay [26]. It is recommended that assays be run 20 times to determine the initial precision/repeatability of the test [26]. Reproducibility should be examined by several labs, all using the same protocol, reagents, and controls on 20 samples [26]. The samples should contain the full range of analyte concentration. The results of each lab should be compared to those of the other labs to determine the reproducibility [26]. The amount that the collective results differ from the actual values should also be considered [26].

- Accuracy- Accuracy for diagnostic tests is defined as the "agreement between a test result and a reference value or an accepted result" [27]. The accuracy of a test can be determined by including standards with known analyte concentration in each run of the assay [26]. The apparent analyte concentration obtained from the output may then be compared against the actual analyte concentration, enabling an individual to determine how accurate the output is [26]. It is recommended that assays be run 20 times to determine accuracy [26]. According to the checklist for 510(k)s, tests for accuracy should include data (where applicable) related to "linearity; calibrator or assay traceability; calibrator and/or assay stability protocol and acceptance criteria; assay cut-off; method comparison or comparison to clinical outcome; matrix comparison; and clinical reference range or cutoff" [28].

- Sensitivity- The requirements for specificity include characterizing the detection limits of the device. Some specific metrics that are required are LoB, LoD, and LoQ [28]. LoB is the Limit of Blank and is the "highest ***apparent*** analyte concentration expected to be found when replicates of a sample containing no analyte are tested" [29]. This is essentially the analytical noise of the assay. LoB is calculated using the following formula:

  $$\mathrm{LoB} = \mathrm{mean}_{\mathrm{blank}} + 1.645(\mathrm{SD}_{\mathrm{blank}})$$ [29]

  The limit of detection (LoD) is the smallest concentration of analyte that can be reliably distinguished from the LoB [29]. This is the concentration at which detection is possible and cannot be attributed to noise. LoD can be found by measuring the mean output of blank replicates (n ~ 20 replicates) and adding two standard deviations to that number [29]. Alternatively, LoD can be calculated by testing the output from a low, known analyte concentration sample [29]. LoD is then determined using the following formula:

  $$\mathrm{LoD} = \mathrm{LoB} + 1.645(\mathrm{SD}_{\mathrm{low\ concentration\ sample}})$$ [29]

  The limit of quantitation (LoQ), is the lowest concentration of analyte that produces a large enough analytical signal so that bias, imprecision, and error are not significantly impacting

the results [29]. LoQ is predetermined based off of the lowest concentration of analyte that produces reliable results. LoQ is usually greater than and sometimes equal to LoD [29].

- Analytical specificity- Analytical specificity is the ability of the diagnostic test to measure the correct analyte, rather than others in the sample [30]. Specificity can be calculated by dividing the number of true negatives, by the sum of the true negatives and false positives [26].

The check list for what should be included in a 510(k) can be found here.

Example 510(k)s:

- Assay and instrument combination template
- 510(k) submission template

PMA

Under 21 CFR 814.20, the following information is required in the submission of a PMA (see Appendix C for an outline of this information):

1. The name and address of the applicant.
2. A table of contents that includes the volume and page number for each item in the table. The nonclinical and clinical sections should be separate. A PMA should be submitted in six copies each bound in one or more numbered volumes no thicker than 2". The applicant should include information that he/she believes is confidential, or financial, or trade secret in each of the copies. In at least one of the copies, the applicant should point at what information he/she believes is confidential.
3. A summary that is detailed enough to impart a general understanding of the information in the application.

   The summary section should be 10 to 15 pages and summarize content found elsewhere in the PMA. The summary should include the following information:

   - Indication for use- Give a description of the disease/condition and the patient population for which the device is intended to be used.
   - Device description- Provide an explanation of how the device works and the scientific concepts that underlie its function. Significant physical and performance characteristics as well as the generic and proprietary names of the device should also be included. A description of the manufacturing process should be included if it markedly enhances one's understanding of the diagnostic test.
   - Alternating practices and procedures- Give a description of available practices/procedures for diagnosing the disease/condition. If similar class III devices are available, include a statement such as "other commercially available devices include…" and then describe the devices.
   - Marketing history- Provide a "brief description of the foreign and U.S. marketing history, if any, of the device, including a list of all countries in which the device has been marketed

and a list of all countries in which the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device. The description shall include the history of the marketing of the device by the applicant and, if known, the history of the marketing of the device by any other person."

The marketing history should contain "dates of introduction into each country, information about the quantity of product distributed in each country, a brief description of any experience reporting mechanism, a summary of any adverse experiences reported, and information about any withdrawals for any reason related to the safety or effectiveness."

- Summary of studies- Summarize results of non-clinical and clinical studies as well as any other relevant technical data related to the safety and effectiveness of the device. The summary must include objectives and hypotheses of each study, experimental design, data collection and analysis method, and results. Clinical summaries should contain the following information: subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and any other relevant data. Studies undertaken as part of an Investigational Device Exemption (IDE) must be acknowledged.

- Conclusions drawn from the studies- Provide a discussion as to why the data included in the application is valid scientific evidence and delivers assurance that the device is safe and effective. This section should also include an explanation of risks and benefits of the device and additional studies that will be conducted after approval of the PMA.

4. A complete description of the device and the following components:
    - Pictorial representations
    - If the device is made up of more than one physical component or ingredient, include a description of the functional components of the device,
    - A description of the properties relevant to diagnosing the disease/condition
    - A description of how the device works
    - "The methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with current good manufacturing practice can make a knowledgeable judgment about the quality control used in the manufacture of the device."
5. Necessary information to prove that the device meets voluntary performance standards and standards established under section 514 of the act or under section 534 of Subchapter C--Electronic Product Radiation Control of the Federal Food, Drug, and Cosmetic Act. It is also necessary to justify any deviations from voluntary standards or the standards outlined in the above acts.
6. Technical sections that include nonclinical and clinical data. The information should be detailed enough so that the FDA is able to make a decision to either approve or deny the application. The nonclinical studies should include results of microbiological, toxicological,

immunological, biocompatibility, stress, wear, shelf life, and other relevant laboratory or animal tests as appropriate. Many of these requirements are not applicable for *in vitro* diagnostic devices. Instead, studies for diagnostic device center around precision/reproducibility, accuracy, sensitivity, and analytical specificity as outlined in the previous 510(k) section.

A separate section should contain the results of clinical studies involving human subjects. In addition to the results, this section should include the following information: clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations. Investigation undertaken as part of an IDE should be identified.

Reports on clinical investigations involving humans must also include "a statement that each study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under 56.104 or 56.105, and that it was conducted in compliance with the informed consent regulations in part 50; or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance." In addition, this section should include "a statement that each study was conducted in compliance with part 812 or part 813 concerning sponsors of clinical investigations and clinical investigators, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance."

7. If data from only one investigation is used to support a PMA, a justification must be included as to how the findings support the safety and effectiveness of the device and why the data is reproducible.
8. A bibliography of all published reports that should be reasonably known to the applicant and are relevant to the safety and effectiveness of the device. This section should also include a discussion of any other available data (foreign or domestic) that should be reasonably well known to the applicant and pertains to the safety and effectiveness of the device.
9. If requested by the FDA, one or more samples of the device. If it is not practical to send the device in, the submitter should provide a location where the FDA can examine the device.
10. Proposed labeling for the device.
11. "An environmental assessment under 25.20(n) prepared in the applicable format in 25.40, unless the action qualifies for exclusion under 25.30 or 25.34. If the applicant believes that the action qualifies for exclusion, the PMA shall under 25.15(a) and (d) provide information that establishes to FDA's satisfaction that the action requested is included within the excluded category and meets the criteria for the applicable exclusion."
12. A financial certification or disclosure statement as outlined in 21 CFR 54.4.

13. Information on pediatric use of the device, including how many pediatric patients are affected by the underlying disease and a description of subpopulations (neonates, infants, children, adolescents) that suffer from the disease the device intends to diagnose/treat.

Source for all of the information in the PMA section: [31]

IDEs and Clinical Studies

Clinical trials are usually required for PMAs, but not 510(k)s. For detailed information on Investigational Device Exemptions (IDEs) and clinical trials for IVDs, click here.

De Novo

The following content should be included in a de novo request:

1. Administrative information- The name, address, phone, and email of the applicant.
2. Regulatory history- List and describe any previous submissions to the FDA. These include previous 510(k)s, not substantially equivalent decisions, Pre-Submissions, and prior de novo requests. The submitter should acknowledge how previous FDA feedback was responded to and implemented.
3. Device information and summary- The submitter must provide the device name, device description, intended purpose, description of all main functions, technological characteristics, components, and accessories. The submitter must also provide instructions on how to use the device and provide information on the target population and disease.
4. Change summary- Provide information on how previous FDA feedback (from prior 510(k)s or Pre-Submissions) was incorporated into the design. The summary should also include information on changes to the device and protocols outlined in the prior submissions.
5. Classification summary- For de novo requests without prior 510(k) submission, include a description of your search for predicate devices. Provide any approved PMAs, regulations, and/or product codes that are similar to your device. Include justification as to why your device is different from and does not fit within any of the aforementioned regulations, PMAs, or similar products.
6. Classification recommendation- Provide a recommendation as to why your device should be Class I or II. Also, justify why general controls (Class I) or general controls along with special controls (Class II) are sufficient to ensure the safe and effective use of your device.
7. Proposed special controls (for Class II devices)- Describe proposed special controls and cross-reference other information within the submission that justifies why the devices meet these controls.
8. Supporting protocols and/or data- Summarize all non-clinical and clinical testing that demonstrates that the device is safe and effective and can be regulated adequately by general controls or general controls in conjunction with special controls. The summary must include objectives and hypotheses of each study, experimental design, data collection and analysis methods, and results. Clinical summaries should include the following information: subject

selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and any other relevant data. Studies undertaken as part of an Investigational Device Exemption must be acknowledged.

9. Summary of benefits- Support the effectiveness of your device. Cite data/studies and published literature that support your conclusions.
10. Summary of known and potential risks to health- Identify health risks and reasons for these risks. Summarize studies that support the safety of your device.
11. Risk and mitigation information- Construct a table of proposed mitigation measures for each risk. Identify whether the mitigation measures fall under general controls or special controls. Provide section and page numbers where the details on each mitigation measure are included in the submission.

    Example table:

Identified Risk	Recommended Mitigation Measures	Supporting Data Contained in De Novo
EXAMPLE: Adverse tissue reaction	Specified Biocompatibility Testing Requirements (special control)	Testing in compliance with recognized standard (Section XX, page XXX)
EXAMPLE: Device failure due to XXX (mechanical failure, software anomaly, use error, etc.)	Specified Performance Testing (special control), Device Specific Labeling Requirements (special control), Medical Device Reporting (MDR) (general control)	Test protocols and results (Section XX, pages XXX) Draft device labeling (Section XX, pages XXX)
EXAMPLE: Failure to properly interpret test results	Device Specific Labeling Requirements (special control)	Draft device labeling (Section XX, pages XXX)

[32]

12. Benefit-risk consideration- Provide an analysis on how the benefits of the device outweigh the possibility of injury or illness.
13. Device labeling- Proposed labeling which conforms to labeling rules.

Source for all of the information in the De Novo section: [32]

Example de novo requests:

- EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay
- EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR FilmArray® Meningitis/Encephalitis (ME) Panel

HDE

Under 21 CFR 814.104, the following information is required for HDE applications:

1. A copy of or reference to the FDA's office of Orphan Products Development decision that the device qualifies as a humanitarian use device.
2. A description of why the filer would be unable to bring the device to market unless he/she is allowed to submit an HDE and a statement that no comparable devices exist to treat/diagnose the condition/disease in question. The application should also include information on the risks and benefits of currently used devices or procedures that diagnose/treat the disease being considered.
3. A discussion of why the benefits of the device outweigh its risks, taking into account the risks and benefits of devices and procedures that are currently used to treat/diagnose the disease in question. The discussion should also include a description of the underlying disease and the mechanism of action of the device.
4. HDEs should contain all of the information required for PMAs. See the PMA section to review these requirements. There are several exceptions to the requirements for PMAs. Instead of including summaries, conclusions, and results from clinical investigations required under 814.20(b)(3)(v)(B), (b)(3)(vi), and (b)(6)(ii), summaries, conclusions, and results of all clinical experiences or investigations reasonably obtained by the applicant should be included in the application. This data should focus on the risks and benefits of the device. Moreover, in addition to the labeling requirements for PMAs, HDE devices must contain the following label: "Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated."
5. The amount charged for the device. If the amount that the device costs exceeds $250, the applicant must include a report from an independent CPA or a responsible individual in the organization that the amount charged for the device does not exceed the cost of the device's research, development, fabrication, and distribution.
6. Information about pediatric uses of the device as set forth in step 13 of the PMA application.

If the applicant believes that any of the above requirements are not applicable for his/her device, a statement that identifies and justifies each omission must be included in the application.

Source for all of the information in the HDE section: [33]

Step four: Send your premarket submission to the FDA

After you have put together the correct premarket submission, the next step is to actually submit it. The submission guidelines are detailed below.

510(k) and de novo- 510(k)/de novo submissions should be put in a temporary, inexpensive binder. The FDA will remove the submission from the binder, 3-hole punch it, and put it in a 3-ring jacket when they review it. The paper that the submission is printed on should be standard

size (8.5” x 11”). The FDA requires two copies of the submission: a paper copy and an electronic copy. Information on the electronic copy can be found here. The 510(k)/de novo submission is not returned after review, so the submitter should retain a copy for themselves. Submission should be sent to the following address:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

The submitter will receive an acknowledgment letter with the 510(k)/de novo number within a week that the FDA receives the submission. The submission must include payment for review fees. Information on review fees can be found here.

Source for all of the above information: [34]

PMA and HDE- Similar to 510(k) submissions, PMA/HDE submissions must be printed on 8.5” x 11” paper with left-hand margins of at least 1.5” wide. This is so the submissions can be put into 3-ring jackets. The submission should be printed on 3-hole punched paper and if it exceeds 2” in thickness, it should be separated into volumes. The submitter should clearly identify the submission as a PMA/HDE application and include a cover letter (Appendix B). The pages should be sequentially numbered and a table of contents should be included. Furthermore, tabs should identify each section. PMA applications are required to includes copies of individual subject reports for each person who died during clinical investigations or did not finish the investigation. To determine what should be included in these reports, the submitter should consult the ODE review division. The PMA/HDE must be signed by the applicant. For information regarding the number of copies and format (paper versus eCopy) of a PMA/HDE submission see the document linked here. PMAs and HDEs for diagnostic devices should be sent to the same address as 510(k)s. See the 510(k) section for this address. More information on how to file a PMA can be found here.

Source for all of the information in the preceding paragraph: [35]

Step five: Register your device and establishment with the FDA

Owners of businesses that produce or distribute medical devices intended for use in the U.S. must register their facility and device annually with the FDA [36]. Registration requires payment of a registration fee [36]. Devices and facilities can be registered online. Those who have not previously registered a device/establishment, will need to create a FURLS account [36]. For detailed information on how to register, click here.

Clinical Laboratory Improvement Amendments

In general, the FDA regulates IVDs; however, laboratory developed tests (LDTs) are not subject to FDA review [37]. LDTs are *in vitro* diagnostic tests that are designed, manufactured, and used within a single laboratory [37]. Due to this lack of oversight, the Clinical Laboratory Improvement Amendment (CLIA) was passed, which gave the Centers for Medicare and Medicaid Services (CMS) the power to regulate LDTs and other IVDs performed in clinical laboratories [37]. Under

CLIA, CMS requires clinical laboratories to be certified before "accepting materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or the impairment of, or assessment of the health of human beings" [37]. CLIA regulations are determined based on test complexity. For FDA approved devices, the test complexity is determined by the FDA during the pre-market approval process [37]. Tests that are developed by laboratories and are not subject to FDA approval are automatically considered high complexity [37]. Under 24 CFR 493.12, Seven areas are examined to determine test complexity and each area is scored 1 (lowest complexity) to 3 (highest complexity). Test that score above 12 points are high complexity, while tests that score lower than 12 points are categorized as moderate complexity. The seven areas that diagnostic tests are evaluated on are shown below:

1. Knowledge- A score of 1 means that to perform the test, the user needs only minimal scientific and technical knowledge and the skills needed to perform the test may be obtained on-the-job. A score of 3 indicates that the test requires specialized scientific and technical knowledge to perform preanalytic, analytic or postanalytic phases of the testing.
2. Training and experience- A score of 1 means that the preanalytic, analytic and postanalytic phases of the testing process require minimal training and only limited experience is needed to perform the test. A score of 3 means that specialized training is required for the preanalytic, analytic and postanalytic phases of the testing process and considerable training is required to perform the test.
3. Reagents and materials preparation- A score of 1 indicates that the reagents used are stable and reliable and do not require special handling or storage conditions. Additionally, the reagents are either prepackaged or premeasured. A score of 3 indicates that the reagents are labile and require special handling or reagent preparation requires manual steps such as volumetric measurements.
4. Characteristics of operational steps- A score of 1 means that the steps are automatically executed or easily controlled. A score of 3 indicates that the operational steps require close monitoring and special specimen preparation, precise temperature control or timing of procedural steps, accurate pipetting, or extensive calculations.
5. Calibration, quality control, and proficiency testing materials- A score of 1 indicates that the calibration, quality control, and external proficiency testing materials (when available) are stable and the quality control and calibration materials are also readily available. A score of 3 indicates that the calibration, quality control, and external proficiency testing materials are labile or quality control materials are not available.
6. Test system troubleshooting and equipment maintenance- A score of 1 indicates that troubleshooting is automatic, self-correcting, clearly described, or requires minimal judgment and maintenance is performed by the manufacturer, is seldom needed or can easily be performed. A score of 3 indicates that the troubleshooting is not automatic and requires decision-making and direct intervention or the maintenance requires special knowledge and skills.
7. Interpretation and judgement- A score of 1 indicates that minimal interpretation and judgment are required to perform preanalytic, analytic and postanalytic phases and problem

resolution requires limited independent judgment. A score of 3 indicates that extensive independent interpretation and judgement are required to perform the preanalytic, analytic and postanalytic phases and problem resolution requires considerable judgment.

Source for all of the CLIA classification information: [38]

Some tests are CLIA-waved, which means the tests are simple with low probability of incorrect results. CLIA-waved tests include FDA approved tests for home use and tests approved for waiver by the FDA during the premarket review process [37]. Laboratories that perform only waived tests must still have a CLIA certificate and follow the manufacturer's instructions; however, the other CLIA requirements are not applicable to them [37]. Laboratories that perform moderate complexity test must meet the requirements set forth by 42 CFR 493, subparts H, J, K, M and Q [39]. Laboratories that perform high complexity test must meet the requirements set forth by 42 CFR 493, subparts F, H, J, K, M, and Q [39].

Appendices

Appendix A

21 CFR Sec. 807.92 Content and format of a 510(k) summary.

"(a) A 510(k) summary shall be in sufficient detail to provide an understanding of the basis for a determination of substantial equivalence. FDA will accept summaries as well as amendments thereto until such time as FDA issues a determination of substantial equivalence. All 510(k) summaries shall contain the following information:

(1) The submitter's name, address, telephone number, a contact person, and the date the summary was prepared;

(2) The name of the device, including the trade or proprietary name if applicable, the common or usual name, and the classification name, if known;

(3) An identification of the legally marketed device to which the submitter claims equivalence. A legally marketed device to which a new device may be compared for a determination regarding substantial equivalence is a device that was legally marketed prior to May 28, 1976, or a device which has been reclassified from class III to class II or I (the predicate), or a device which has been found to be substantially equivalent through the 510(k) premarket notification process;

(4) A description of the device that is the subject of the premarket notification submission, such as might be found in the labeling or promotional material for the device, including an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material used, and physical properties;

(5) A statement of the intended use of the device that is the subject of the premarket notification submission, including a general description of the diseases or conditions that the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is intended. If the indication statements are different from those of the legally marketed device identified in paragraph (a)(3) of this section, the 510(k) summary shall contain an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and why the differences do not affect the safety and effectiveness of the device when used as labeled; and

(6) If the device has the same technological characteristics (i.e., design, material, chemical composition, energy source) as the predicate device identified in paragraph (a)(3) of this section, a summary of the technological characteristics of the new device in comparison to those of the predicate device. If the device has different technological characteristics from the

predicate device, a summary of how the technological characteristics of the device compare to a legally marketed device identified in paragraph (a)(3) of this section.

(b) 510(k) summaries for those premarket submissions in which a determination of substantial equivalence is also based on an assessment of performance data shall contain the following information:

(1) A brief discussion of the nonclinical tests submitted, referenced, or relied on in the premarket notification submission for a determination of substantial equivalence;

(2) A brief discussion of the clinical tests submitted, referenced, or relied on in the premarket notification submission for a determination of substantial equivalence. This discussion shall include, where applicable, a description of the subjects upon whom the device was tested, a discussion of the safety or effectiveness data obtained from the testing, with specific reference to adverse effects and complications, and any other information from the clinical testing relevant to a determination of substantial equivalence; and

(3) The conclusions drawn from the nonclinical and clinical tests that demonstrate that the device is as safe, as effective, and performs as well as or better than the legally marketed device identified in paragraph (a)(3) of this section.

(c) The summary should be in a separate section of the submission, beginning on a new page and ending on a page not shared with any other section of the premarket notification submission, and should be clearly identified as a "510(k) summary."

(d) Any other information reasonably deemed necessary by the agency.”

Appendix B

Original PMA Cover Letter

[Date]

PMA Document Mail Center - WO66-G609
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

SUBJECT: Original PMA for *[device trade name and model number if applicable]*

To Whom It May Concern:

[Applicant's name] is submitting this original premarket approval application for the *[device trade name], [device generic name]* intended for use in *[indication for use]*.

Clinical studies of the above device were initiated on *[date]* and *[were/were not]* conducted under an approved investigational device exemption *[give IDE number if a significant risk device]*. [If applicable, include the FDA reference number for any premarket notification, reclassification petition, or color additive petition submitted for this device].

[Include a paragraph providing the name and address of each facility involved in the manufacture of the device and indicate whether the facility is prepared for an FDA inspection. If not prepared, provide an expected date when the facility will be ready for inspection. If a waiver of the QS information is requested, provide an anticipated date that the information will be provided.]

If another document is incorporated by reference, e.g., a master file, please include the original letter of authorization as an attachment to this cover letter.

The existence of this PMA and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed. [*Tip*: confidentiality claims cannot be made unless the applicant has complied with the applicable requirements.

If there are questions regarding this submission, *[name]* may be contacted at *[give telephone number including area code]*.

Sincerely yours,

[signature]

[Name and title of applicant's representative]

Appendix C

PMA Content Outline:

I. General Information
    - Device generic name
    - Device trade name
    - Applicant's name and address
    - PMA number*
    - Date of Panel recommendation*
    - Date of notice of approval to the applicant*
    - (*to be completed by FDA unless known to the applicant)

II. Indications for Use

III. Device Description

IV. Contraindications, Warnings, and Precautions

V. Alternative Practices and Procedures

VI. Marketing History

VII. Potential Adverse Effects of the Device on Health
    - Tip: Include any information concerning actual or potential adverse effects that the device may have on health (e.g. if an implanted device, discuss the fate of the device in the body)

VIII. Summary of Preclinical Studies
    - Laboratory studies
    - Animal studies
    - Additional studies

IX. Summary of Clinical Studies
    - Study design
    - Patient assessment
    - Demographic data
    - Data analysis and result
    - Device failures and replacements

X. Conclusions Drawn from the Studies
    - Risk/benefit analysis
    - Safety
    - Effectiveness

XI. Panel Recommendations (To be completed by FDA)

XII. CDRH Decision (To be completed by FDA)

XIII. Approval Specifications (To be completed by FDA)

References

[1] Miller, Curt. "Bringing a New Medical Device to Market." *Minnesota Physician*. N.p., Nov. 2007. Web. 16 Oct. 2016.

[2] Fripp, G. "A Step-by-step Guide to Segmenting a Market." *Market Segmentation Study Guide*. N.p., 2016. Web. 16 Oct. 2016.

[3] "Competitive Analysis." *SMALL BUSINESS ENCYCLOPEDIA*. Entrepreneur, n.d. Web. 16 Oct. 2016.

[4] Knowles, Michael. "How to Write a Competitive Analysis." *Michael Knowles Consulting*. N.p., 2002. Web. 16 Oct. 2016.

[5] "Barriers to Entry: Factors Preventing Startups from Entering a Market." *MaRS Library*. MaRS, 06 Dec. 2013. Web. 16 Oct. 2016.

[6] Arline, Katherine. "PEST Analysis: Definition, Examples & Templates." *Business News Daily*. N.p., 11 Dec. 2014. Web. 16 Oct. 2016.

[7] "General Information concerning Patents." *United States Patent and Trademark Office*. N.p., Oct. 2015. Web. 16 Oct. 2016.

[8] Taylor, Daniel A. "BitLaw." *Patent Requirements. http://www.bitlaw.com/patent/requirements.html*. N.p., n.d. Web. 16 Oct. 2016.

[9] "General Information concerning Patents." *United States Patent and Trademark Office*. USPTO, Oct. 2015. Web. 16 Oct. 2016.

[10] Stim, Rich. "Types of Patents." *Nolo.com*. N.p., n.d. Web. 16 Oct. 2016.

[11] *7-Step U.S. Patent Search Strategy Guide*. Alexandria: USPTO, n.d. PDF.

[12] "Provisional Application for Patent." *United States Patent and Trademark Office*. USPTO, n.d. Web. 16 Oct. 2016.

[13] "Nonprovisional (Utility) Patent Application Filing Guide." *United States Patent and Trademark Office*. USPTO, Jan. 2014. Web. 16 Oct. 2016.

[14] Stim, Rich. "Patent Claims: The Basics." *NOLO.com*. NOLO, n.d. Web. 17 Oct. 2016.

[15] "Process for Obtaining a Utility Patent." *United States Patent and Trademark Office*. USPTO, n.d. Web. 17 Oct. 2016.

[16] "Standard Practice Guide Policies." *University of Michigan Technology Transfer Policy*. University of Michigan, Oct. 2015. Web. 17 Oct. 2016.

[17] FEDERAL FOOD, DRUG, AND COSMETIC ACT, §§ 5-513-513 (2002). Print.

[18] Serrano, Katherine. *FDA Regulation of In Vitro FDA Regulation of In Vitro Diagnostic Tests*. Silver Spring: FDA, 19 July 2010. PDF.

[19] "How to Study and Market Your Device." *Device Advice: Comprehensive Regulatory Assistance*. FDA, 16 Sept. 2015. Web. 17 Oct. 2016.

[20] *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*. Silver Spring: FDA, 13 July 2012. PDF.

[21] "Premarket Notification 510(k)." *U.S. Food and Drug Administration*. FDA, 15 Sept. 2016. Web. 17 Oct. 2016.

[22] "Premarket Approval (PMA)." *U.S. Food and Drug Administration*. FDA, 28 July 2016. Web. 17 Oct. 2016.

[23] "Evaluation of Automatic Class III Designation (De Novo) Summaries." *U.S. Food and Drug Administration*. FDA, 28 Sept. 2016. Web. 17 Oct. 2016.

[24] "Humanitarian Device Exemption." *U.S. Food and Drug Administration*. FDA, 4 June 2015. Web. 17 Oct. 2016.

[25] Code of Federal Regulations Title 21, §§ 1-807-807 (2016). Web.

[26] Jacobson, R. H. *PRINCIPLES OF VALIDATION OF DIAGNOSTIC ASSAYS FOR INFECTIOUS DISEASES1*. New York: Search Results U.S. Fish and Wildlife Service, n.d. PDF.

[27] "Accuracy/Bias." *Medical Devices: A Primer for Developers and Investors*. LabDataAnalysis.com, n.d. Web. 17 Oct. 2016.

[28] *Refuse to Accept Policy for 510(k)s*. Silver Spring: FDA, 1 Oct. 2015. PDF.

[29] Armbruster, David A, and Terry Pry. "Limit of Blank, Limit of Detection and Limit of Quantitation." *The Clinical Biochemist Reviews* 29.Suppl 1 (2008): S49–S52. Print.

[30] Saah AJ, Hoover DR. "Sensitivity" and "Specificity" Reconsidered: The Meaning of These Terms in Analytical and Diagnostic Settings. Ann Intern Med. 1997;126:91-94.

[31] CFR - Code of Federal Regulations Title 21, §§ 1-814.20-814.20 (2016). Web.

[32] *De Novo Classification Process (Evaluation of Automatic Class III Designation)*. Silver Spring: FDA, 14 Aug. 2014. PDF. *http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf*

[33] CFR - Code of Federal Regulations Title 21, §§ 1-814.20-814.20 (2016). Web. *https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.104*

[34] "How to Prepare a Traditional 510(k)." *U.S. Food and Drug Administration*. FDA, 28 Dec. 2015. Web. 17 Oct. 2016.

[35] "PMA Review Process." *U.S. Food and Drug Administration*. FDA, 27 July 2016. Web. 17 Oct. 2016.

[36] "How to Register and List." *U.S. Food and Drug Administration*. FDA, 9 Jan. 2016. Web. 17 Oct. 2016.

[37] Lee, Y. C. *Development and Validation of In Vitro Diagnostic Tests*. Vancouver: PACGEN, n.d. PDF.

[38] 42 CFR, §§ IV-493.17-493.17 (1993). Web. *https://www.law.cornell.edu/cfr/text/42/493.17*

[39] 42 CFR, §§ IV-493.25-493.25 (2003). Web. *https://www.law.cornell.edu/cfr/text/42/493.25*